

Claims

1. A method for the production of an aromatic or hetroaromatic fluorine-labelled compound comprising fluoridation of an iodonium salt with a fluoride ion source characterised in that the reaction solvent comprises water.
2. A method as claimed in claim 1, wherein the reaction solvent is 100% water.
3. A method as claimed in claim 1 wherein the reaction solvent is a mixture of water and a water miscible solvent.
4. A method as claimed in claim 3, wherein the water miscible solvent is acetonitrile, ethanol, methanol, tetrahydrofuran or dimethylformamide.
5. A method as claimed in claim 3 or claim 4 wherein the volume:volume ratio of water:water-miscible solvent is between 1:99 and 1:1.
6. A method as claimed in claim 5 wherein the volume:volume ratio of water:water-miscible solvent is from 10:90 to 30:70.
7. A method as claimed in any one of claims 1 to 6, wherein the fluoride ion source is potassium, caesium or sodium fluoride.
8. A method as claimed in any one of claims 1 to 7 for the fluoridation of an iodonium salt of Formula (I) or (II):



wherein:

Q is an electron deficient aromatic or heteroaromatic moiety;

each of R¹, R², R³, R⁴ and R⁵ is independently hydrogen, -O(C₁₋₁₀ alkyl) or C₁₋₁₀ alkyl; and

Y⁻ is a counter ion such as trifluoromethane sulfonate (triflate), perfluoro C₂-C₁₀ alkyl sulphonate, trifluoroacetate, methane sulfonate (mesylate), toluene sulfonate (tosylate), tetraphenylborate;

to give a product of general formula (III):



where Q is as defined for general formulae (I) and (II).

9. A method as claimed in claim 8, wherein each of R¹-R⁵ is independently selected from hydrogen, C₁₋₃ alkyl and -O-(C₁-C₃ alkyl).

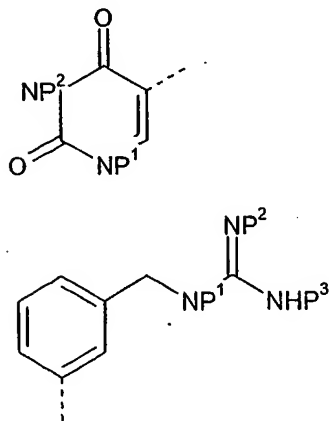
10. A method as claimed in claim 8 or claim 9 wherein, in the compound of Formula II, the "solid support" is polystyrene, polyacrylamide, polypropylene or glass or silicon coated with such a polymer.

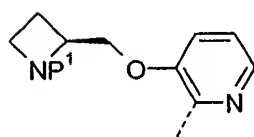
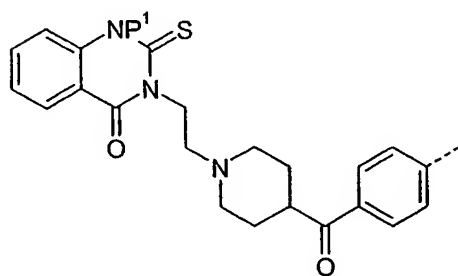
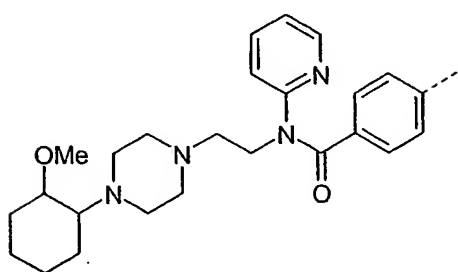
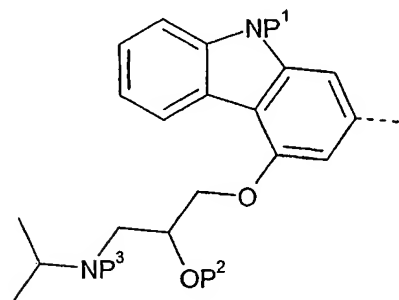
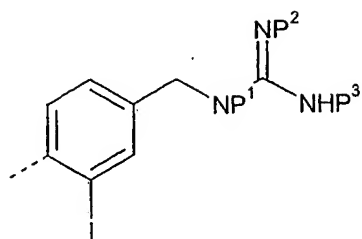
11. A method as claimed in any one of claims 8 to 10 wherein the solid support is in the form of small discrete particles or is a coating on the inner surface of a reaction vessel.

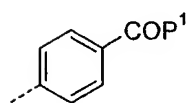
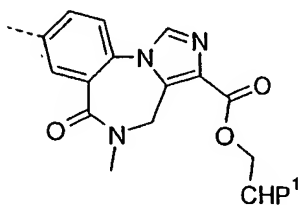
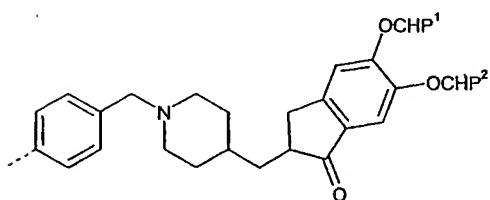
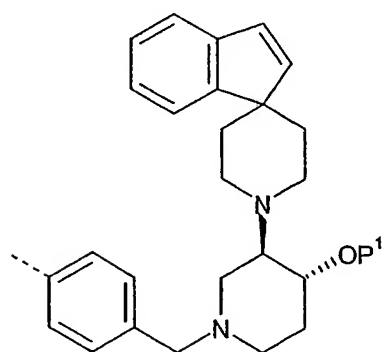
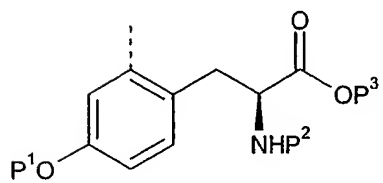
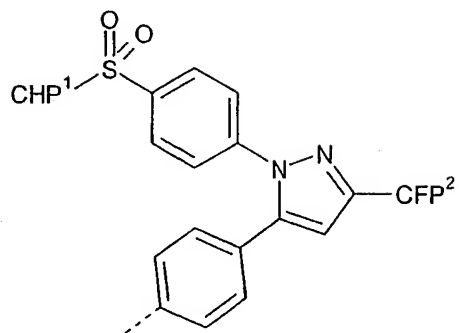
12. A method as claimed in any one of claims 8 to 11, wherein, in the compound of Formula II the "linker" is C₁₋₂₀ alkyl or C₁₋₂₀ alkoxy, attached to the resin by an amide ether or a sulphonamide bond or a polyethylene glycol (PEG) linker.

13. A method as claimed in any one of claims 8 to 12 wherein the aromatic group Q is substituted with one or more substituents selected from C₁₋₁₀ alkyl, -O(C₁₋₁₀ alkyl), -C(=O) C₁₋₁₀ alkyl, -C(=O)NR⁶(C₁₋₁₀ alkyl), -(C₁₋₆ alkyl)-O-(C₁₋₆ alkyl), C₅₋₁₄ aryl, -O(C₅₋₁₄ aryl), -C(=O)C₅₋₁₄ aryl, -C(=O)NR⁶(C₅₋₁₄ aryl, C₅₋₁₄ heteroaryl, -O(C₅₋₁₄ heteroaryl), -C(=O)C₅₋₁₄ heteroaryl, -C(=O)NR⁶(C₅₋₁₄ heteroaryl), C₃₋₁₀ cycloalkyl, -O(C₃₋₁₀ cycloalkyl), -C(=O)(C₃₋₁₀ cycloalkyl), -C(=O)NR⁶(C₃₋₁₀ cycloalkyl), C₃₋₁₀ heterocyclyl, -O(C₃₋₁₀ heterocyclyl), -C(=O)(C₃₋₁₀ heterocyclyl), -C(=O)NR⁶(C₅₋₁₄ heterocyclyl),
 5 wherein R⁶ is H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ heterocyclyl, C₄₋₁₀ aryl or C₄₋₁₀ heteroaryl;
 any of which may optionally be substituted with OH, NHR⁶, COOH or protected versions any of these groups; or alternatively
 any two adjacent substituents may form a four- to six-membered carbocyclic or heterocyclic ring, optionally fused to a further aromatic, heteroaromatic,
 15 carbocyclic or heterocyclic ring.

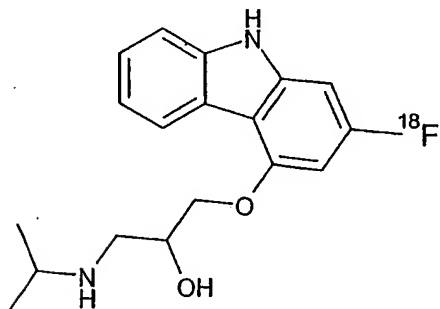
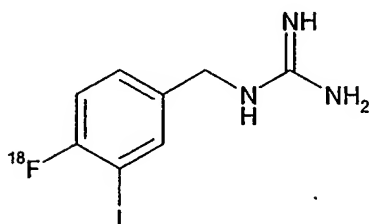
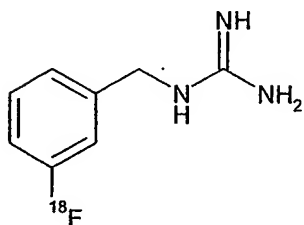
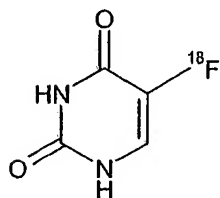
14. A method as claimed in claim 13, wherein the aromatic moiety Q has an additional substituent selected from OH, NHR⁶ or halogen.
- 20 15. A method as claimed in any one of claims 8 to 14, wherein the group Q is one of the following:

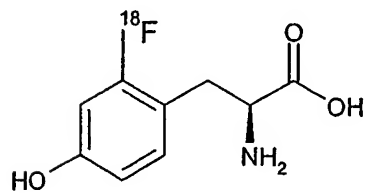
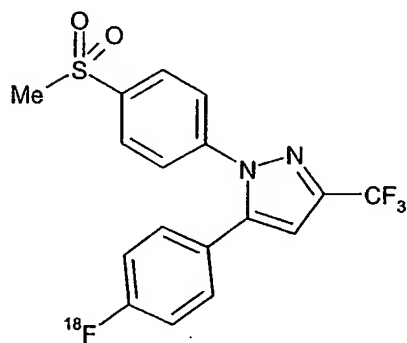
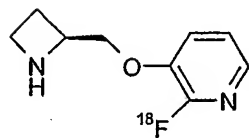
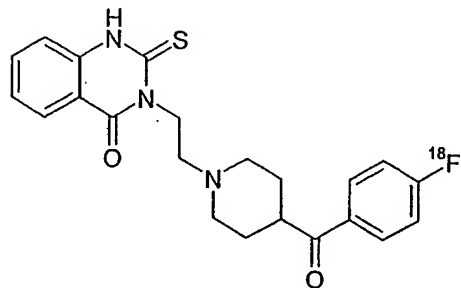
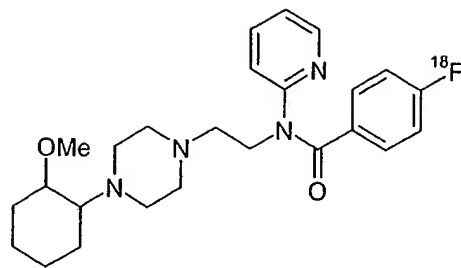


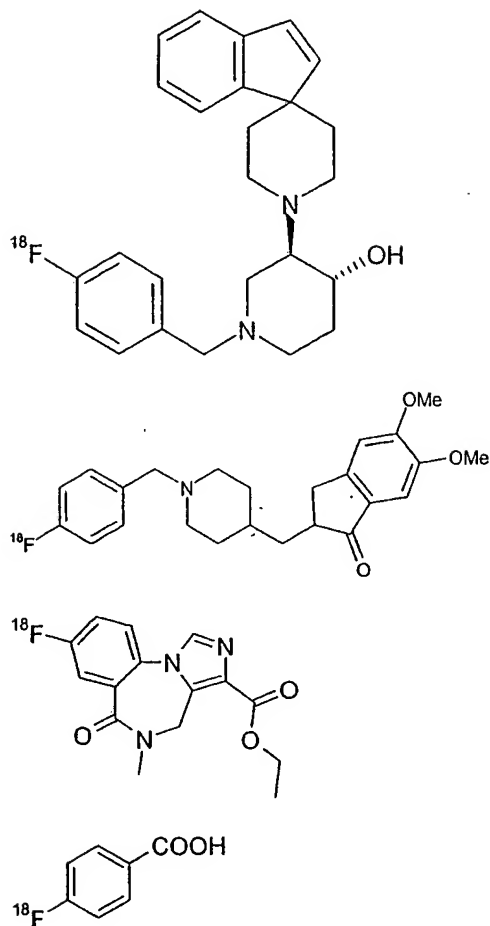




16. A method as claimed in any one of claims 1 to 18, wherein the fluorine-labelled compound is an [^{18}F]-labelled compound and the fluoride ion source is a source of $^{18}\text{F}^-$.
- 5 17. A method as claimed in claim 15 or claim 16, wherein the F-labelled compound is selected from the following:







18. A method as claimed in any one of claims 1 to 17, further including, in any order, one or more of the following steps: removal of excess $^{18}\text{F}^-$, for example by ion-exchange chromatography; and/or
- (i) removal of the protecting groups; and/or
 - (ii) removal of organic solvent; and/or
 - (iii) formulation of the resultant compound as an aqueous solution.

19. A kit for the production of an aromatic fluorine-labelled compound, the kit comprising:

- (i) a vial containing an aqueous solvent for dissolving the fluoride ion source; and

(ii) a reaction vessel containing an iodonium salt.

20. A kit as claimed in claim 19, wherein the solvent is 100% water.

5 21. A kit as claimed in claim 19 wherein the solvent is a mixture of water and a water miscible solvent.

22. A kit as claimed in claim 21, wherein the water miscible solvent is acetonitrile, ethanol, methanol, tetrahydrofuran or dimethylformamide.

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23. A kit as claimed in claim 21 or claim 22 wherein the volume:volume ratio of water:water-miscible solvent is between 1:99 and 1:1.

15 24. A kit as claimed in claim 23 wherein the volume:volume ratio of water:water-miscible solvent is from 10:90 to 30:70.

25. A kit as claimed in any one of claims 19 to 24 wherein the iodonium salt is compound of general formula (I) or (II) as defined in any one of claims 8 to 15.

20 26. A kit as claimed in claim 20 wherein the iodonium salt is a compound of general formula (II) as defined in any one of claims 8 to 15 and the solid support comprises a coating on the surface of the reaction vessel.

25 27. A kit as claimed in any one of claims 19 to 26, wherein the reaction vessel is a cartridge or a microfabricated vessel.

28. A kit as claimed in any one of claims 19 to 27, further comprising a source of fluoride ions.